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Palladium-catalysed Carbomethoxyvinylation and Thienylation of 5-Iodo(Bromo)-2,4-Dimethoxypyrimidine in Water

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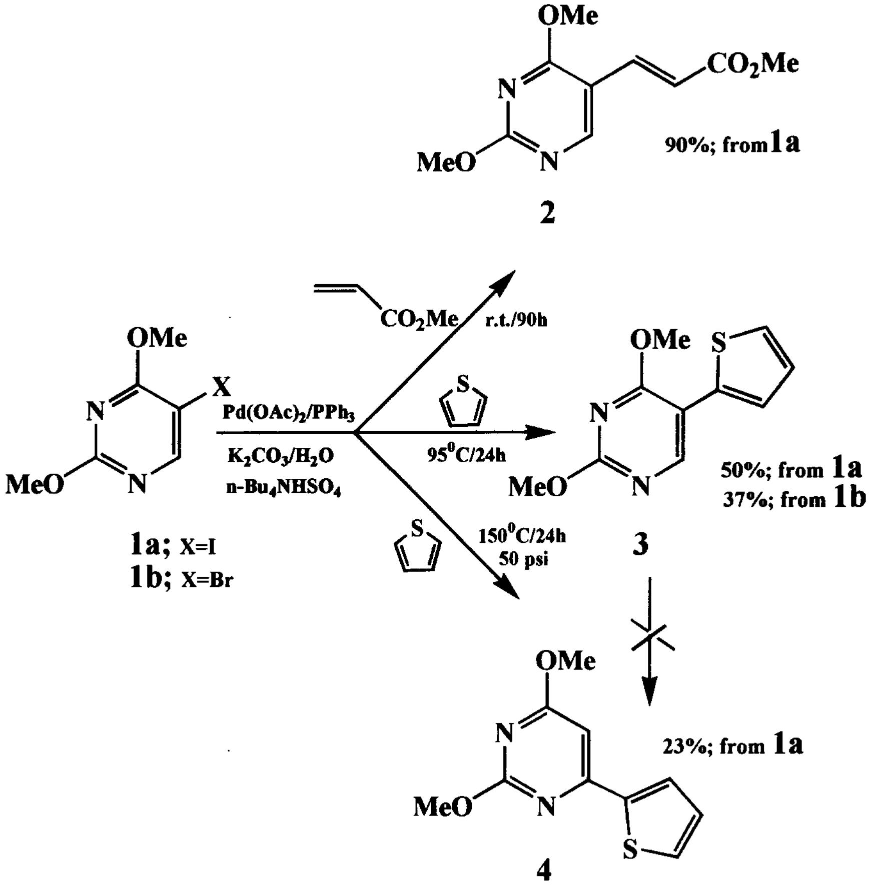
Abstract : (*E*)-5-(2-Carbomethoxyvinyl)-2,4-dimethoxypyrimidine (**2**) was prepared in high yield (90%) at room temperature from 5-iodo-2,4-dimethoxypyrimidine (**1a**) *via* the heterogenous Heck-reaction with methyl acrylate in aqueous solution containing n-Bu_4NHSO_4 and potassium carbonate. Under the same conditions, using thiophene and heating the mixture under reflux, 5-(2-thienyl)-2,4-dimethoxypyrimidine (**3**) was obtained in 50% yield starting from **1a**, or in 37% yield starting from 5-bromo-2,4-dimethoxypyrimidine (**1b**). Surprisingly, the use of **1a** and thiophene at 150^0 C in a pressure reactor (50 psi) resulted in a 23% yield of 6-(2-thienyl)-2,4-dimethoxypyrimidine (**4**) only. © 1997 Elsevier Science Ltd.

For our programme of the synthesis of new 5-substituted 2'-deoxyuridines and 4'-thio-2'-deoxyuridines[1] we needed a reliable and efficient method to obtain different 5-heteroaryl(vinyl)-substituted 2,4-dimethoxypyrimidines. A method which was previously used for the large scale preparation of (*E*)-5-(2-bromovinyl)-2,4-dimethoxypyrimidine from 5-bromo-2,4-dimethoxy-pyrimidine, was rather lengthy (4 steps), low-yielding (23% overall) and was not applicable to the preparation of 5-heteroaryl-2,4-dimethoxypyrimidines.[2] The key intermediate in this synthetic sequence, (*E*)-5-(2-carbomethoxyvinyl)-2,4-dimethoxypyrimidine (**2**) was also prepared on a small scale in a good yield (78%) from 5-iodo-2,4-dimethoxypyrimidine (**1a**), employing "classical" Heck-chemistry under strictly dry conditions.[2] With the intention of developing a simple, high yielding and reproducible method for the large scale preparation of compound **2**, we turned our attention to Heck-type chemistry in water.[3] Palladium-catalyzed carbomethoxyvinylation of iodobenzene in water in the presence of base and a phase-transfer catalyst (PTC) provided *trans*-methyl cinnamate in 98% yield.[4] In this study we present our results from the application of similar conditions for carbomethoxyvinylation and 2-thienylation of compound **1a(1b)**; the results are summarized in Scheme 1.

Vinylation of the compound **1a** with methyl acrylate under mild conditions (r.t./90h) gave a reproducible isolated yield of 90% of the expected product **2**.[5] When the same reaction was repeated at 50^0 C, the starting material **1** was consumed after 5h and product **2** was isolated in 79% yield.

Thienylation of the compound **1a** with thiophene at room temperature gave no reaction but when heated under reflux (95^0C /24h) gave an isolated yield of 50% of the expected thienyl product **3**[6]. All the starting material **1a** was consumed and the reaction mixture contained small amounts of another three UV-absorbing compounds, which were not identified. When the reaction was repeated with less reactive bromoderivative substrate **1b**, the product **3** was obtained in 37% isolated yield only (Scheme 1).



Scheme 1

In an attempt to improve the yield of the product **3** from **1a**, different conditions of thienylation were investigated. When thienylation was repeated at 50°C, after 80h of intensive stirring, a small amount of compound **1a** was still present, and the product **3** was isolated in only 29% yield while the reaction mixture again contained small amounts of the three above-mentioned UV-absorbing sideproducts.

Several recent papers have demonstrated a rate enhancement of the palladium-catalysed coupling reactions under pressure[7-9] and rapid and highly selective reactions in pure superheated water have also been reported.[10] Therefore, thienylation was repeated in the closed system of a pressure reactor, where the reaction mixture was stirred at 150^{0}C under a pressure of 50psi for 24h. All the starting material **1a** was consumed and an unexpected major product **4** was isolated in 23% yield.[11] The reaction mixture contained at least eight other UV-absorbing compounds, which were not identified.

Compared with carbomethoxyvinylation, thienylation of compound **1a(1b)** is a more complex reaction and yields are effected by several variables such as the reaction time, temperature and pressure. The results obtained so far, indicate that a longer reaction time and a higher temperature, accelerate decomposition of both the starting material **1a(1b)** and the products **3** and **4**. At the same time, higher pressure seems to be involved in the changed regioselectivity.[8] Compound **4** cannot be produced from compound **3** under these reaction conditions.

The identity of products **3** and **4** was established unequivocally (^{1}H and ^{13}C NMR, nOe, MS, UV, X-ray crystal structure and elemental analysis for compound **3**). The significant differences in chemical shift-values (in particular those of ^{13}C NMR) and in UV-spectra of both compound **3** and **4** explain the rather surprising visible-light photolability (and fluorescence properties) of compound **4**, compared to the photostable compound **3**. Compound **4** is extremely unstable and cannot be purified.

Thus using activated olefins, substitution of 5-iodo-2,4-dimethoxypyrimidine can occur at position 5 giving high reproducible yields of the corresponding 5-vinyl analogue at room temperature in aqueous solution. With less reactive substrates reasonable yields can be obtained when the reactions is heated under reflux but when subjected to a pressure of 50psi, only unexpected 6-substituted derivative was produced in low yield.

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5. K_2CO_3 (20.5g; 148mmol), n-Bu_4NHSO_4 (20.5g; 60.4mmol), water (60ml) and $Pd(OAc)_2$ (950 mg; 4.2mmol, 0.07 equiv. on **1a**) were successively added to an intensively stirred mixture of **1** (16g; 60.1mmol), methyl acrylate (21g; 242mmol) and PPh_3 (2.2g; 8.4mmol). Stirring was continued at room temperature for 90h, the reaction mixture was diluted with 300ml of dichloromethane, washed with water (3x300ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified on a silica-column with n-hexane:ethyl acetate (1:1; v/v), to give 12.1g (90%) of pure **2**. ^{1}H NMR [δ(ppm)] in DMSO-d_6 : identical with literature[2], in $CDCl_3$: 8.38 (1H, s, H-6), 7.60 (1H, d, J = 16 Hz, vinylic), 6.62 (1H, d, J = 16 Hz, vinylic), 4.09 (3H, s, -OCH_3), 4.03 (3H, s, -OCH_3), 3.80 (3H, s -CO_2CH_3).

6. K_2CO_3 (13.6g; 100mmol), n-Bu_4NHSO_4 (13.6g; 40mmol), water (40ml) $Pd(OAc)_2$ (640mg; 2.8mmol, 0.07 equiv. on **1a**) was added to a mixture of **1a** (10.6g; 40mmol), thiophene (17g; 203mmol) and PPh_3 (1.48g; 5.6mmol). The resulting reaction mixture was stirred under reflux (oil bath, 95^{0}C) for 24h. The cooled reaction mixture was then diluted with 400ml of CH_2Cl_2, washed with water (4x200ml), dried ($MgSO_4$) and evaporated. The residue was purified twice times on a silica column using ethyl acetate:n-hexane as solvent (first 1:1, then 1:4). Upon combination and evaporation of the homogenous fractions, a crystalline product **3** was obtained in three crops giving an overall yield of 50%. ^{1}N NMR [δ(ppm)] in $CDCl_3$: 8.51 (1H, s, H-6), 7.42 (1H, dd, $J_{3'4'}$ = 4Hz, $J_{3'5'}$ = 2 Hz, 3'-thienyl), 7.34 (1H, dd, $J_{5'4'}$ = 6 Hz, $J_{5'3'}$ = 2 Hz, 5'-thienyl), 7.10 (1H, dd, $J_{4'3'}$ = 4 Hz, $J_{4'5'}$ = 6 Hz, 4'-thienyl), 4.11 (3H, s, $-OCH_3$), 4.04 (3H, s, $-OCH_3$); ^{13}C NMR [δ(ppm)] in $CDCl_3$: 167 (C-2), 164 (C-4), 156 (C-6), 134 (C-2', thienyl), 127 and 125 (C-3', 4' and 5', all-thienyl), 110 (C-5), 55 and 54 (both $-OCH_3$); MS (EI): 222 [M^+]; UV (EtOH): λ_{max} = 276 nm (ε = 20 200), shoulder at 300 nm; For $C_{10}H_{10}N_2O_2S$: Calculated C = 54.04 %, H = 4.54 %, N = 12.60 %, S = 14.43; Found C = 54.29 %, H = 4.81 %, N = 12.31 %, S = 14.27 %.

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11. K_2CO_3 (6.8g; 50mmol), n-Bu_4NHSO_4 (6.8g; 20mmol), water (20ml), $Pd(AcO)_2$ (320mg; 1.4 mmol, 0.07 equiv. on **1a**), were successively added to **1a** (5.3g; 20mmol), thiophene (8.5g; 102 mmol) and PPh_3 (740mg; 2.8mmol) in a mechanically stirred steel pressure-reactor (PARR INSTRUMENT Co., Model 4561, 300ml volume). The reactor was closed and the reaction was carried out with intensive stirring at 145^{0}C (oil bath) for 24h. The pressure created inside reactor was 50psi. The cooled reaction mixture was diluted with 200ml of CH_2Cl_2, washed with water (4x100ml), dried ($MgSO_4$) and evaporated. The residue was purified twice on a silica column, first with ethyl acetate, then with ethyl acetate:n-hexane (1:1). Upon evaporation of the homogenous fractions, a crystalline product **4** was obtained in three crops giving an overall yield of 1g (23%). ^{1}H NMR [δ(ppm)] in $CDCl_3$: 7.55 (1H, s, H-5), 7.37 (1H, dd, $J_{3'4'}$ = 4 Hz, $J_{3'5'}$ = 1.5 Hz, 3'-thienyl), 7.30 (1H, dd, $J_{5'4'}$ = 5.5 Hz, $J_{5'3'}$ = 1.5 Hz, 5'-thienyl), 7.04 (1H, dd, $J_{4'3'}$ = 4 Hz, $J_{4'5'}$ = 5.5 Hz, 4'-thienyl), 3.50 (3H, s, $-OCH_3$), 3.44 (3H, s, $-OCH_3$); ^{13}C NMR [δ(ppm)] in $CDCl_3$: 156 (C-2), 146 (C-4), 133 (C-5), 129 (C-2', thienyl), 122, 120 and 118 (C-3', 4' and 5', all-thienyl), 104 (C-6), 32 and 23 (both-OCH_3); MS (EI): 222 [M^+]; UV (EtOH): λ_{max} = 262 nm (ε = 10 200), 319 nm (ε 9 660).

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